REMARKS

Claims 1-20 are cancelled. Claims 21-38 are pending.

Preliminary Matters.

This amendment is in response to the Office communication dated October 29, 2004 relating to the present application. The communication acknowledged that Applicants' amendment dated March 16, 2004 ("the March 16 Amendment") was a *bona fide* attempt to respond to the prior Office Action, but was deemed not fully responsive the Office Action. The communication asserts that the newly presented claims are allegedly drawn to an invention outside the scope of the examined invention. In particular, the communication stated that "the formula of claim 12 does not have the same limitation at residue 9 found in the originally examined claims and all claims are missing the negative limitation found in the originally examined claims." The communication also indicated that the March 16 submission did not address all of the rejections of record.

The Applicants respectfully submit that the statements on page 4 of the prior, non-final Office Action (dated November 17, 2003) under the "Claim Objections" heading indicate a misunderstanding of the nature of the claimed invention. The Office Action states that "...claim 1 requires that the sequence not be from a native HBV surface protein" (emphasis added). This statement is incorrect. Actually, claim 1 stated: "Wherein CPP is no native HBV surface protein." The word "from" was not present in claim 1. Claim 1 utilized the transitional phase "comprises", which absent the negative limitation would have encompassed full-length native HBV surface proteins within the scope of the claims. The negative limitation, however, did not exclude oligopeptides "from" HBV proteins, did not exclude "HBV-derived" peptides, and did not exclude fragments of HBV proteins from the scope of the claim. In fact, small, 12-amino acid oligopeptides, including those which have an amino acid sequence that overlaps with a 12-amino acid portion of an HBV protein sequence, are preferred embodiments of the invention.

In the *bona fide* interest of expediting prosecution, however, claims 12-20 have been cancelled without prejudice to the filing of a continuing application directed to the subject matter thereof. Remaining claims 21-38 all fall within the scope of original claim 1, as properly construed. Independent claims 21 and 30 are directed to 12-amino acid oligopeptides that were

within the scope of claim 1, as explained above. The oligopeptides of claim 21 encompasses 12-amino acid oligopeptides in which the amino acid residue at each position in the polypeptide is defined by the sign of the hydropathy value of the amino acid. Claim 21 simply utilizes an alternative to the "hydrophobic/hydrophilic/charged" nomenclature that was objected to in original claim 1. Accordingly, the oligopeptides of claim 21 are a subset of the peptides of original claim 1, which encompassed 12-amino acid oligopeptide, as well as longer polypeptide materials. Similarly, claim 30 is directed to specific 12-amino acid oligopeptides also within the scope of claim 21 and original claim 1. Dependent claims 22-29 and 31-38 are directed to fusions of the oligopeptides of claim 21 and 30, respectively, with various classes of polypeptides. The fusion proteins of claims 22-29 and 31-38 also fall within the scope of original claim 1, which was a very broad generic claim.

The negative limitation statement of original claim 1 is missing from claims 21-38 because it is unnecessary. Oligopeptides consisting of only 12 amino acids, *de facto*, are not native HBV proteins, because native HBV proteins have many more than 12-amino acid residues. Similarly, the fusion proteins of the dependent claims, *de facto*, are not native HBV proteins. Fusion proteins are artificial constructs, and the proteinaceous fusion partners recited in the claims are not HBV structures. Accordingly, the negative limitation of original claim 1 is properly omitted from the present claims.

Claim Objections.

Claim 2 was objected to as being of allegedly improper dependent scope for failing to further limit the subject matter of a previous claim. Although Applicants do not agree with this characterization, claim 2 has been cancelled rendering the foregoing objection moot.

Claim Rejections under 35 U.S.C. §112.

Claims 1 and 2 were rejected as being indefinite, because the formula recited in claim 1 was allegedly unclear. The Office Action stated that it is not clear which amino acids are specified by the notations i, o, and x in the formula, since asparagine and glutamine are listed twice, as hydrophilic amino acids and as charged amino acids. It is well known that charged

amino acids are hydrophilic. One of ordinary skill in the art at the time the invention was made would have understood that the hydrophilic amino acids of the formula include the charged amino acids as well. The recited limitations, therefore, were not ambiguous. In any event, the cancellation of claims 1 and 2 render this rejection moot.

New claim 21 replaces claim 1. As noted above, this claim does not recite a formula, does not use the "hydrophobic/hydrophilic/charged" terminology, and does not include a negative limitation. Rather, claim 21 defines the invention in an alternative format. The claim is directed to a 12-amino acid oligopeptide defined in terms of the signs of the hydropathy values of the amino acids. The claim is supported by the description in the specification on pages 2 and 3 and in the figures, as noted in the March 16, 2004, Amendment. The hydropathy values of amino acids are well known to those of ordinary skill in the art (see, for example, page 112 of the well known biochemistry textbook by Lehninger *et al.* entitled *Principles of Biochemistry*, Second Edition, Worth Publishers, (1993), submitted herewith, and listed on accompanying form PTO/SB/08B). The choice of amino acid residue for each position in the 12-amino acid residues of the oligopeptide is clearly defined and definite. Claim 30 is directed to specific, preferred oligopeptides defined by sequence identifier numbers. Clearly, claim 30 is definite. Claims 22-29 and 31-38 are directed to fusion proteins of the 12-amino acid oligopeptides fused to various, well known proteinaceous materials. All of the present claims are clear and definite.

Claims 1 and 2 were also rejected as lacking a written description that would have conveyed to one of ordinary skill in the art that the inventors had possession of the claimed invention. The Office Action stated, at page 6: "The claims are drawn to a motif that enables a peptide to be cell permeable wherein it is not a native HBV surface protein. . . .The written description in this case only sets forth sequences of surface proteins of native HBVs. The sequences in the figures are <u>from</u> known HBVs." (emphasis added). As noted above, the scope of the original claims included oligopeptides "from HBV"; only full-length native HBV proteins were excluded from claim 1.

Claim 21 is directed to an oligopeptide *consisting of* 12-amino acid residues, wherein each of the amino acid residues is defined by the sign of its hydropathy value. These oligopeptides, when attached to a long polypeptide molecule, i.e., having more than 12-amino

acid residues, such as a protein or protein fragment, render the longer polypeptide cell permeable. Applicants developed this invention through analysis of the structures of known, full length HBV proteins, which are cell permeable.

Present claims 21 and 30 are directed to small, 12-amino acid residue oligopeptides, not to large polypeptides such as full length HBV proteins. Among the preferred oligopeptides of the invention are the segments of natural HBV proteins, which Applicants discovered impart cell permeability. The specification contains a clear written description of examples of oligopeptides within the scope of the claims. Claim 21, therefore, is a generic claim directed to these oligopeptides, and the support for claim 21 was set forth in the March 16 Amendment. Preferred examples of the oligopeptides of claim 21, shown in the figures, are specifically claimed in claim 30. Claims 22-29 and 31-38 are directed to fusion proteins of the oligopeptides of claim 21 and 30, respectively, fused to various protein materials. These fusion proteins are also described in the specification as noted in the of March 16 Amendment.

Claims 1 and 2 were additionally rejected for alleged lack of enablement. The last paragraph of page 7 of the Office Action acknowledges that the specification is "... enabling for DHBV derived cell permeability mediating peptide"... . Preferred embodiments of the oligopeptides of claim 21, e.g., those set forth in claim 30, are indeed "HBV-derived" peptides, in that the amino acid residue sequence of the oligopeptide overlaps with a 12-amino acid portion of a full length HBV protein. *A fortiori*, claim 31 is enabled.

Furthermore, the examples provided in the specification, in combination with the known hydropathy values of amino acids, would have enabled one of ordinary skill in the art at the time the invention was made to prepare any 12-amino acid oligopeptide that falls within the scope of claim 21. The sign (positive or negative) of the hydropathy value at each position dictates the final structure and the function of the product. The fact that claim 21 covers a large genus does not, in itself, negate enablement. The nature of the claimed invention is a 12-amino acid oligopeptide that is useful for enhancing cell permeability when attached to other peptide molecules. The signs of the hydropathy values of the amino acid residues of the oligopeptide dictate the functional utility of the compound. The preparation of 12-amino acid oligopeptides has been routine in the chemical arts for decades and methods for carrying out such preparations

are well known. The hydropathy values of the amino acids (and whether the value is positive or negative) are also well known. Little or no experimentation would have been required to prepare an oligopeptide of claim 21 or claim 30 at the time the invention was made, since the amino acid residue for each of the 12 residues of the oligopeptide is clearly defined by known hydropathy values, and the methods for preparing such small oligopeptides were routine. Accordingly, claim 21 and claim 30 are clearly enabled by the specification.

With regard to claims 22-29 and 31-38, methods of fusing small oligopeptides to larger proteins are also well known and referred to in the specification. The specification provides methods for evaluating cell permeability of a given fusion protein. As noted above, the oligopeptides to be fused with the proteins are defined and enabled. The classes of materials to be fused with the oligopeptides are known protein materials. Any experimentation involved in preparing such fusion proteins would have been routine for one of ordinary skill in the art. Thus, claims 22-29 and 31-38 are enabled, as well.

Rejections for Anticipation.

Claims 1 and 2 were rejected as being anticipated by Wieprecht, *et al.*, (cited in the Information Disclosure Statement). While Applicants do not agree with the basis of the rejection, the rejection was rendered moot in any case by the cancellation of claims 1 and 2. The cited Wieprecht reference does not apply to the present claims. Present claim 21 is directed to a 12-amino acid oligopeptide of specified structure, which is useful for imparting cell permeability to other materials when bonded to such materials. Wieprecht does not teach or suggest a 12-amino acid oligopeptide at all, much less one of the specified structure and properties. Nor does Wieprecht teach or suggest the specific 12-amino acid oligopeptides of claim 30. Accordingly, neither claim 21 nor claim 30 is anticipated by Wieprecht.

With regard to claims 22-29 and 31-38, Wieprecht cannot teach or suggest fusing an oligopeptide of claim 21 or 30 to the various protein materials set forth in the claims, since the oligopeptides themselves are not taught or suggested.

Conclusion.

Applicants submit that the present pending claims 21-38 fall within the scope of the invention searched, i.e., original claim 1, and are patentable under 35 U.S.C. 112 and over the applied art. All issues set forth in the Office Action having been addressed, Applicants respectfully request reconsideration and early allowance of all claims.

Respectfully submitted,

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